TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OBSTETRICS AND GYNECOLOGY DEVICES PANEL

62nd MEETING

Pages 1 thru 293

Gaithersburg, Maryland
January 24, 2000

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Monday, January 24, 2000

9:00 a.m.

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P A R T I C I P A N T S

Jorge Blanco, M.D., Panel Chair
Elisa Harvey, D.V.M., Ph.D., Executive Secretary

Panel Voting Members:

Donald Chatman, M.D.
Subir Roy, M.D.
Nancy Sharts-Hopko, Ph.D.
Machelle Allen, M.D.
Ralph D'Agostino, Ph.D.
Mike Diamond, M.D.
Gary Eglinton, M.D.
Jay Iams, M.D.
Michael Neuman, Ph.D., M.D.
Mary Jo O'Sullivan, M.D.
Robert Wolfson, Ph.D., M.D.

Industry Representative

Gary Jarvis

Consumer Representative

Diony Young

C O N T E N T S

P R O C E E D I N G S

CHAIRMAN BLANCO: Let's go ahead and get started. There are a couple of panel members who are on the way in, so we will go through some of the preliminaries so that we can stay on time. This is a lot of information and a lot of things that we are going to be doing today, so we need to try to make sure that we get going. We want to make sure that we stay on time, and it is very important that we give all the appropriate time to the PMA that we are evaluating today.

I would like to go ahead and formally call the meeting to order. I want to remind everyone that there is a sign-in sheet by the door. If you would please sign in, let us know who you are and who was here.

Before we have a strict agenda, and there is a time period for comments from the audience. We know of two organizations, people, that want to speak before the panel. If you would like to speak before the panel, that is the time to do it. If you feel like you would like to make a comment during the panel deliberations, you must be recognized. We do not accept outbursts from the audience, and any time that you are coming forward to speak, you need to come to the mike and identify yourself. You need to identify whether you have any conflicts of interest. That means if any organization, company, etc. has funded any or

part of your trip, research, or any other possible conflict of interest, you really need to let us know for the record what that relationship is.

At this time, I would like to just go around through the panel and have everyone introduce themselves to the audience, and if we can go ahead and start from this left side.

MR. JARVIS: Gary Jarvis, the industry representative.

MS. YOUNG: I am Diony Young, the consumer representative from Genesco, New York.

DR. ROY: Subir Roy, from the University of Southern California.

DR. SHARTS-HOPKO: Nancy Sharts-Hopko, from Villanova University.

DR. DIAMOND: Michael Diamond, Professor of Obstetrics and Gynecology, Wayne State University in Detroit.

DR. IAMS: Jay Iams, obstetrician from Ohio State University.

CHAIRMAN BLANCO: I am Jorge "George" Blanco, the University of Florida at Pensacola.

DR. HARVEY: I am Elisa Harvey, from the Center for Devices. I am the Executive Secretary for the Obstetrics and Gynecology Devices Panel.

DR. EGLINTON: Gary Eglinton, New York Hospital, Queens.

DR. O'SULLIVAN: Mary Jo O'Sullivan, University of Miami, OB-GYN.

DR. WOLFSON: Robert Wolfson, Colorado Springs, OB-GYN/Perinatology.

MS. ALLEN: Machelle Allen, OB-GYN, NYU, Bellevue.

DR. D'AGOSTINO: Ralph D'Agostino, Boston University, biostatistician.

DR. CHATMAN: Donald Chatman, obstetrician-gynecologist, Northwestern University.

DR. NEUMAN: Michael Neuman, from the Joint Program in Biomedical Engineering of the University of Tennessee and the University of Memphis.

DR. SCHULTZ: I am Dan Schultz. I am the Acting Director of the Division of Reproductive, Abdominal, and Radiological Devices, Office of Device Evaluation, Center for Devices, FDA.

CHAIRMAN BLANCO: All right. Thank you very much. I also would like to let everyone know that Dr. Dan Schultz, the Acting Division Director, is the FDA press contact, and if anyone would like some press information, he is the person to get in touch with. Now Dr. Harvey is going to do some more of the preliminaries.

DR. HARVEY: I would like to start by reading a

couple of documents. One is the appointment to temporary voting status for today:

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990 and amended April 20, 1995, I appoint the following people as voting members of the Obstetrics and Gynecology Devices Panel for the duration of this panel meeting on January 24, 2000: Dr. Machelle Allen; Dr. Ralph D'Agostino; Dr. Michael Diamond; Dr. Gary Eglinton; Dr. Jay Iams; Dr. Michael Neuman; Dr. Mary Jo O'Sullivan; and Dr. Robert Wolfson. For the record, these people are special government employees and are consultants to this panel. They have undergone the customary conflict of interest review and they have reviewed the material to be considered at this meeting.

And it is signed by Dr. David Feigal, the Director of the Center for Devices and Radiological Health.

The second document I would like the put into the record is the conflict of interest statement for this meeting:

The following announcement addresses conflict-of-interest issues associated with this meeting and is made a part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial

interests reported by the committee participants. The conflict-of-interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest.

However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government. A waiver has been granted for Dr. Donald Chatman for his interest in firms that could potentially be affected by the panel's deliberations. The waiver allows him to participate fully in all matters before the panel today.

Copies of this waiver may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Michael Neuman and Robert Wolfson. These individuals reported past or current interests in firms at issue, but in matters not related to the topics for today's session. Therefore, the agency has determined that they may participate fully in the deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant

should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

The other things I would like to point out are that there is information on getting transcripts and videos of today's meeting at the table at the back of the room.

Anyone who has any comments to make to the panel, if you could provide a hard copy with your remarks, that would be helpful. Mr. Mike Kuchinsky, at the podium, will take those from you.

The last thing I would like to point out is, for the panel's sake, what the panel folder contents are so that they can follow through today's proceedings. You should have a copy of the agenda, the discussion questions, and the panel roster, as well as the presentations for today. I will be giving some information on regulatory definitions. You have the sponsor's presentation in your folder. You have presentations from FDA, by Kathy Daws-Kopp and Diane Mitchell. You have some information from a representative of ACOG, and you have a previous statement that was made to the OB-GYN Devices Panel in 1996 by Dr. Larry Gilstrap.

Thank you.

CHAIRMAN BLANCO: Thank you, Dr. Harvey. All right. It's my pleasure now to begin the meeting by introducing Mr. Colin Pollard, Chief of the Obstetrics and Gynecologic Devices Branch, who will give us some information.

Introductory Comments

MR. POLLARD: Thank you, Dr. Blanco. Good morning, ladies and gentlemen of the panel, distinguished audience.

We have brought you together today to consider the premarket approval application, or PMA, submitted by the Nellcor Perinatal Business of Mallinckrodt, for its intrapartum fetal oxygen saturation monitoring system, the Nellcor N-400.

The sponsor has proposed that this monitor be indicated for women who are in labor with term pregnancies when the strip-chart tracing from conventional intrapartum fetal monitoring is non-reassuring. Immediately following my opening remarks, Dr. Harvey, Executive Secretary of your panel, will go over the basic ground rules of your panel deliberations on this PMA, especially with respect to what constitutes valid scientific evidence, safety, and effectiveness.

I don't think I need to tell you that we consider

this a very important PMA. With nearly four million births in the U.S. each year, the currently proposed indication for this new sensor may impact more than a quarter of that number.

Some of you will recall that we convened this panel three-and-a-half years ago, in July of 1996, to consider this technology and others like it in a general way. We, at FDA, wanted to develop a guidance document that would help manufacturers and clinical researchers put together cogent clinical development plans for products like this.

At that meeting, Nellcor shared its plan with the panel for the pivotal clinical study that would support its future PMA. Besides the FDA-invited guest speakers, several other manufacturers and researchers also addressed the panel.

You should know that we have put issuance of this draft guidance document aside for the moment so that we can digest how this first PMA goes and the panel input on it.

From a regulatory viewpoint, our meeting today is a natural progression from our 1996 meeting, because we are now going to look at the data from that clinical study to see whether it supports approval of that PMA. I bring to your attention that two other PMAs will hinge on the outcome of this PMA before you today. These two secondary PMAs are

from GE\Marquette and Agilant Technologies, who will integrate the Nellcor fetal pulse oximetry technology into their currently marketed fetal monitors, the Corometrics and Hewlett-Packard monitors, respectively.

Although there certainly is important information and data for FDA to review in these two secondary PMAs to ensure that the technology is integrated properly, we do not plan to bring either of them before the panel and they are not the subject of today's agenda.

We have tried our best to bring together a truly top-notch panel, with experts in instrumentation and biostatistics, not to mention extensive representation by perinatologists. We are fortunate to have here today many of the same panel participants from that 1996 meeting, including our panel chair, Dr. Blanco, as well as Dr. Eglinton, Dr. Neuman, Dr. Allen, and Dr. Diamond. We believe that this will add some regulatory continuity to our review process.

Because this product potentially represents a big step for intrapartum clinical management in the U.S., we also strengthened the perinatology expertise on the panel by adding maternal fetal medicine specialists, Dr. Iams, Dr. O'Sullivan, and Dr. Wolfson.

You should also know that, using one of our newer PMA approaches, Mallinckrodt/Nellcor submitted this PMA in a

shell/module configuration. As our review team will explain to you later this morning, this allowed us to review and close out a number of modules of preclinical information.

So, as you well know, the PMA at this point is based primarily on a couple of key clinical studies, including a pivotal randomized control trial that looks at the effect of the new monitor on intervention.

My only point here is that there is a lot of data here and the study results are complex. The panel is a little larger than usual, and you have to work your way completely through the agenda in the limited amount of time we have today. We have impressed upon your panel chair, Dr. Blanco, the importance of due process and the need to arrive at a panel recommendation at the end of the day that conforms to one of the three formats that Dr. Harvey will explain to you in a minute.

To achieve that end, I only ask that we all stay focused, keep our remarks succinct, and respect each other's views. If we succeed with those three things, Dr. Blanco's job will be a lot easier, and we have a very good chance for a successful outcome for this meeting.

I don't want to take up any more of your time, so my comments are concluded. Thank you, Dr. Blanco.

CHAIRMAN BLANCO: Thank you, Colin. We will try to rise to the occasion and ensure that we fulfill your

expectations. I think Dr. Harvey is now going to speak to us on some regulatory issues.

Regulatory Issues

DR. HARVEY: Mike should be putting this up on the slide, if he can, but you have the full handout in your folder as well. I want to provide for the panel and the audience reminders of the regulatory definitions that we are obliged to adhere to today.

The first is valid scientific evidence. Valid scientific evidence is evidence from well-controlled investigations, partially-controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with the marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

The definition of safety: There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from the use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

The definition of effectiveness is that there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

I also want to point out that your PMA review should be independent of cost, any previous regulatory difficulties, clinical data submitted in any other PMAs, or the medical-legal climate and its effect on the standard of care.

At the end of the day, you will be voting on this premarket approval application, and your options will be one of the three: The first is you will vote for recommendation of approval with no conditions attached to the approval. A second option will be approvable subject to specified conditions, and these are such as resolution of very clearly identified deficiencies cited either by you, the panel, or FDA staff. Examples could include resolutions of questions concerning some of the data or changes in the draft labeling.

You may conclude that post-approval requirements should be imposed as a condition of approval. These

conditions may include a continuing evaluation of the device and submission of periodic reports. If you believe that such requirements are necessary, your recommendation must address the following points: The reason or purpose of the requirement; the number of patients to be evaluated; and the reports required to be submitted.

Your third voting option will be not approvable, and if you vote in that way, you must have one of the following reasons for recommending not approvable: Either safety -- and that is that the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling; or effectiveness -- reasonable assurance has not been given that the device is effective under the conditions of use in the labeling; and third, labeling -- based on a fair evaluation of all the material facts in your discussions, you believe the proposed labeling to be false or misleading.

Thank you, Dr. Blanco.

CHAIRMAN BLANCO: Thank you, Dr. Harvey. I just would like to add to that, having been at some of these a few times before, for the new panel members especially, that after your vote, you are also asked to spend a few minutes justifying why you voted the way you did, or at least trying to explain for the record the way that you voted.

We are moving along very nicely, and it is now time for the public comments. At this time, I have two individuals who have requested time for public comment. I again would like to remind these individuals to please note any conflict of interest. I also would like to remind them to keep their notes to the allotted five minutes for each individual.

The first individual that I have is Dr. Susan Ramin, who I believe is representing the American College of Obstetricians and Gynecologists. Is that correct?

Open Public Hearing

MS. RAMIN: Good morning. My name is Dr. Susan Ramin from the University of Texas, Houston Medical Center, and I do not have any conflict of interest.

Let's begin with basically just a brief background in fetal pulse oximetry. It is a new technology that, hopefully, has the potential to aid in evaluating the fetus. It specifically measures -- or at least in the simplest terms, it measures the level of oxygen in the fetus. And this is important because lack of oxygen during labor can result in neurologic damage and cerebral palsy in a newborn.

Now, currently, our ability to monitor or to evaluate or assess fetal well-being includes monitoring the fetal heart rate, either by auscultation or electronically, and also the use of fetal scalp blood pH.

When we look at electronic fetal heart rate monitoring, which was developed in the late 1960s, it was hoped that it would decrease the incidence of cerebral palsy and neonatal mortality but, unfortunately, as we have discovered over the last three decades, this has not done so. The reason for this is because the electronic fetal heart rate monitor is sensitive but it is not very specific.

In other words, a normal fetal heart rate pattern does predict a good neonatal outcome, however, an abnormal pattern is a poor predictor of fetal acidosis, with a 50 percent predictive value. More importantly, most newborns who have an abnormal pattern will be normal.

Electronic fetal heart rate monitoring, however, has been associated with an increase in the cesarian delivery rate, and thus the reason for the development of fetal pulse oximetry, in order to try to help determine which fetus is actually compromised and whether or not intervention needs to be done.

I would like to state a quote by Benson and colleagues, back in 1968, regarding fetal heart rate auscultation: Naivete and wishful thinking inspired our hope for a simple rule-of-thumb estimate of fetal distress. Obviously, the problem is much too complex for such an early appraisal. And I think this holds true for electronic fetal heart rate monitoring, as well.

Moving on with fetal scalp blood pH as a means of assessing fetal well-being, this, too, is a cumbersome technique. It is invasive. It does require multiple determinations, and it has been abandoned by many clinicians. And thus, pulse oximeters have been utilized recently, with past studies and ongoing research.

Now, there are two different types of sensors. There is the transmission sensor and the reflectance sensor, and both measure the amount of oxyhemoglobin absorbed and not absorbed.

When we look at the transmission pulse oximetry, this is utilized with both the adults and also children. This technique utilizes a light-emitting diode that's placed directly across from the photo detector, and it is now currently used routinely in anesthesia, in critical care, and in newborn nurseries. And, I think there is little question that this has been a significant impact on decreasing morbidity and mortality in these settings.

Now, this is just a picture from the article by Lien (phonetic) and Tom Garite in Contemporary OB-GYN, illustrating the transmission sensor, where the device is basically put over a patient's finger. It has been shown to be accurate and has proven efficacy and safety.

Now, for obvious reasons, one cannot utilize transmission pulse oximetry, and therefore reflectance pulse

oximetry has been developed, where both the light emitters and the photo detectors are on the same surface and they measure the amount of light that is reflected back. Again, from the Contemporary OB-GYN article, this illustrates where both are on the same surface.

And, this is again a picture just illustrating where placement of the fetal pulse oximeter, the sensor, is placed through the cervix and fits up against the fetal cheek. This device has been tested in several studies and appears to provide an adequate signal in at least 50 to 60 percent of the time.

So, in simple terms, the fetal pulse oximetry measures not only the arterial oxygen saturation, but it also measure fetal heart rate and peripheral perfusion.

I would like to go over the background or at least the animal studies, especially using the sheep model that has looked at the fetal pulse oximeter. What the animal studies have shown is that the arterial oxygen saturation does seem to correlate with the oxygen that is measured directly in the blood. And, more importantly, the cut-off value of 30 percent, which we are going to discuss again in a few minutes, seems to be less than 30 percent. In other words, in these fetuses, aerobic metabolism is maintained until the arterial oxygen saturation falls below 30 percent, and then metabolic acidosis begins.

When we look at the human studies, the first one reported by Dildy and colleagues in 1994, looking at 160 women who had a normal, spontaneous vaginal delivery, there does appear to be a wide range of arterial oxygen values, and, as we would expect, there is a decrease in the arterial oxygen saturation during labor.

In the first stage of labor, the mean arterial oxygen saturation was 59 percent, and during the second stage of labor, the mean is 53 percent. And if we look at two standard deviations below the mean, the arterial oxygen saturation is 33 percent. Moreover, over 95 percent of all the arterial oxygen saturation values were greater than 30 percent.

In another study, by Steelbach and Gobel in 1995, of 122 women in labor, they found that the duration of decreased arterial oxygenation is also important in predicting newborn outcomes. In fact, what they reported was that when the arterial oxygen saturation fell below 30 percent for more than 10 minutes, the umbilical artery pH was less than 7.20 in more than half of the cases.

So this leads us to the clinical efficacy data, and the big question is does it impact upon detecting the compromised fetus and does it decrease the cesarian delivery rate? Recently, Steve Bloom and Ken Levino in Dallas reported their results of using the fetal pulse oximetry for

intrapartum outcome in the Obstetrics and Gynecology Journal, in 1999.

They utilized this device in 129 fetuses from uncomplicated pregnancies that were 36 weeks gestation or greater, and found that 53 percent had at least one or more episodes of an arterial oxygen saturation of less than 30 percent. They found no difference, however, between the high oxygen saturation and the low oxygen saturation group as far as the rate of cesarian delivery, 13 percent versus nine percent, and there was no difference in the umbilical artery pH of less than 7.20, 10 percent versus 9 percent.

However, they looked at the duration of an arterial oxygen saturation of less than 30 percent for greater than or equal to 2 minutes, and they found that it was associated with an increase in fetal compromise, i.e., cesarian delivery for non-reassuring fetal heart rate tracing and umbilical artery pH of less than 7.2, admission to the special care nursery and 5-minute Apgar scores of 3 or less.

Now, when you look at Nellcor's data, they had 472 women in their baseline phase and then 1190 women in their pilot study and randomized clinical trial. And, it is important to note that in enrollment two-thirds of the women had at least one or more risk factors for subsequent cesarian delivery, and one-third of the fetuses had a risk

factor.

They found that there was no difference in the overall cesarian delivery rate, however, the rate for cesarian delivery for a non-reassuring fetal heart rate tracing was decreased by 50 percent, from 10 percent to 5 percent. They also found that there was a decrease by 43 percent for non-reassuring fetal heart rate tracing and dystocia.

So, the company's data does appear to show that there is a decrease in the cesarian delivery rate for a non-reassuring fetal heart rate tracing.

Then, we have to ask the question about the safety data. Although it is difficult to ascertain safety from the available literature, there are no reports of significant morbidity to either the mother or the fetus.

This technology does not appear to be associated with an increase in infection, as reported by Johnson and colleagues in 1994. Looking at 112 women with a fetal pulse oximeter compared to matched controls, the infectious morbidity rate was the same.

When we look at the company's data, the device, again, does not appear to be associated with significant morbidity, and adverse events appear to be minor. Importantly, there were no maternal deaths and, as reported by Nellcor, maternal adverse effects include fever, mucus

membrane disorder, urinary retention, endometrial disorder, postpartum hemorrhage and anemia.

As far as fetal adverse effects are concerned, again, they were considered mild but included ecchymosis, accidental injury, jaundice, perinatal disorder and dyspnea.

There were 10 adverse events that related to the device, primarily accidental injury, and there were 6 neonatal deaths. Again, the investigators thought that there was no causal relationship to these neonatal deaths and the use of the device. Four of these babies had a cardiac congenital anomaly.

According to Nellcor, significantly more mothers in the fetal heart rate and the fetal pulse oximetry group in the randomized clinical trial had no adverse events, 70 percent versus 66 percent, and there were no adverse maternal events that were considered by the investigators to have a causal relationship with this device.

I think the questions and areas of needed research include peer review of the entire set of data, and then we need to ask the question of whether or not this pulse oximetry device has an impact on neonatal morbidity and mortality, and importantly, doesn't have an impact on long-term neurological outcome.

Another question we must ask is does the reduction in the cesarian delivery rate for non-reassuring fetal heart

tracing -- is that due to other factors, other than the device itself? What is the cost of the technology, and is it only beneficial for high risk patients?

The current recommendation would that if the data holds up to peer review, the reduction in cesarian delivery for non-reassuring fetal heart tracing would appear to justify its approval and use at least in the high risk population because it would have a significant impact on the practice of obstetrics, especially considering the high cesarian delivery rate in this country. It might also potentially have an impact on the high rate of litigation cases for babies that have neurologic dysfunction.

Thank you very much.

CHAIRMAN BLANCO: Dr. Ramin, are you representing ACOG?

DR. RAMIN: I am representing ACOG.

CHAIRMAN BLANCO: Thank you.

DR. RAMIN: That is correct.

CHAIRMAN BLANCO: The next speaker that I have on the list is Susan Meikle -- I apologize if I mispronounced your name -- representing the National Institutes of Health.

MS. MEIKLE: Good morning. My name is Susan Meikle. I am currently the Acting Program Officer for the Maternal-Fetal Medicine Unit Network for NICHD. I have no conflicts of interest.

The Network is a group of thirteen academic institutions, two of which are represented by panel members, who perform protocols. The main objective of the Network was originally to study the etiology of prematurity. This has since evolved over almost fifteen years of evaluation and studies and funding from NICHD to include the areas of low birth weight, medical complications such as asthma, and interventions during labor and delivery.

Some of the studies that are currently undergoing are using magnesium to reduce cerebral palsy; multiple dose steroids versus single dose steroids is something we will do in the future; and we do have a cesarian section registry to look at current rates of cesarian section and those outcomes.

These studies are chosen by the steering committee which is composed of principal investigators, and at our next steering committee meeting the results of this meeting will be presented to the PIs, and I assume that there will be some discussion about interest in that work and looking into some of the questions that were presented by ACOG.

Thank you.

CHAIRMAN BLANCO: Thank you very much. There have been a couple of questions for Dr. Ramin. Would you mind going back to the podium? Did you participate in the study at all?

DR. RAMIN: I did not.

CHAIRMAN BLANCO: Do you have any connection?

DR. RAMIN: I have no connection.

CHAIRMAN BLANCO: Okay, thank you. I would also like to remind the panel that the data being presented today -- the sponsor and the FDA will be the responsible folks to present the data that we need to assess for the panel deliberations.

I do not have anyone else registered to speak. Does anyone from the audience care to make any comments? This is the time to make the public comments.

[No response]

Then, we will use the time wisely and proceed on with our sponsor presentation.

Sponsor Presentation

Introduction and Proposed Indication for Use

MS. PAGE: Good morning. My name is Donna Page. I am employed by Mallinckrodt as a Senior Regulatory Affairs Manager for their Perinatal Division, located in Pleasanton, California.

It is had been a long time coming and we are really pleased to be here today, to present the N-400 Fetal Oxygen Saturation Monitoring System for the panel's consideration.

We have provided the panel with an outline of our

program. We have six key speakers following me. They will each introduce themselves fully at the beginning of their presentation. We also have a lot of information to share with you today so we respectfully request that you hold all questions until the speakers have finished their presentations. To facilitate the question and answer period, we have provided the panel with a list of our attendees and their areas of expertise.

For the record, the N-400 is a pulse oximetry system. It is designed to be used during labor and delivery to continuously monitor the oxygen saturation of the fetus. It is to be used as an adjunct to standard fetal heart rate monitoring.

The system consists of a monitor, a patient module and a sterile sensor. We do have a system here. We are hoping that you will all take the opportunity to take a closer look at it.

For the past four years, the N-400 has been the subject of a clinical investigation under IDE G95106. The results of this clinical investigation will be the focus of our presentation today.

While under investigation in the U.S., the N-400 has been commercially available in the international marketplace. It was introduced to Europe in 1996 with the CE Mark. More recently, it has obtained TGA approval in

Australia, CSA approval in Canada, and is the subject of a pending Shonin application in Japan. It has been well received by the obstetrical community. It has also been thoroughly researched and is the subject of over 300 publications. Since we introduced the product, we have shipped over 35,000 sensors, and we believe that it has been used in a similar number of labors.

Based on the results of Mallinckrodt's clinical investigation, and supported by its history of use in other markets, Mallinckrodt is requesting marketing approval for the N-400 under PMA P990053, with labeling that we believe will be supported by the data and information presented here today.

The next slide shows the components of our indications for use statement. The statement is equivalent to the statement that was in your packet, however, it has been reformatted to more clearly identify the essential elements. The essential elements are the Nellcor N-400 system is intended for use as an adjunct to fetal heart rate monitoring. It is not intended to replace conventional fetal heart rate monitoring during labor.

The patient population for which the N-400 system is intended consists of term infants in active labor, with ruptured membranes, with a non-reassuring fetal heart pattern. The purpose of the N-400 system is to improve the

physician's ability to assess the fetal status. The N-400 directly measures the fetal oxygen saturation. This permits the safe continuation of labor during periods of non-reassuring fetal heart and reassuring FSpO2, reducing the rate of C-sections performed for the indication of non-reassuring fetal status without causing injury to the mother or fetus.

Finally, the addition of the N-400 to conventional fetal heart rate monitoring improves the sensitivity and specificity for matching the delivery indication to immediate neonatal condition.

This concludes my introductory remarks. I would now like to turn the podium over to Dr. David Swedlow. Dr. Swedlow will be providing you with more information on the N-400 technology and discussing the rationale for the 30 percent critical threshold.

Technology and Critical Threshold

DR. SWEDLOW: Good morning. My name is David Swedlow. I am a pediatrician and an anesthesiologist, and I specialize in critical care medicine, until about 1987, when I left academic medicine to join Nellcor as a Senior Vice President of Medical Affairs and Technology Development. I was there for nine years, working on this project and others, until I retired two years ago, and I am currently a paid technical adviser to the company for this project.

The journey for me to today, to fetal pulse oximetry, actually begins 28 years ago, when I was a pediatric house officer at Johns Hopkins. I remember being called in the middle of the night from the neonatal nursery to run down four flights of stairs, run over two buildings, and run up five flights of stairs, which is not easy for me, to attend to the delivery as a pediatrician of a patient being sectioned for fetal distress. I arrived to see anxious, concerned parents and anxious obstetrical house staff, only to be rewarded by a totally normal child.

I thought to myself at that time that there must be a better way of determining who is in trouble and who is not in trouble, but at the time there really wasn't any. Six years later, as an anesthesia resident at the University of Pennsylvania, I was again called in the middle of the night but this time to administer anesthesia for a crash C-section for an emergency delivery. Once again, the baby came out fine but at that time there was no technology available to better define and improve fetal assessment.

In 1982, ten years after the beginning of this story, I saw for the first time a pulse oximeter. It was a device that wrapped a little band-aid around the finger, shone light through the finger and measured the color of blood and, in so doing, measured the oxygen saturation of the patient. At that point in time, I was absolutely

convinced that it would change the practice of medicine, and I thought to myself when I first saw it that this is what we need for the babies, but it has been a long time coming.

Pulse oximetry addresses a very serious medical problem, and that is uncertain patient oxygenation. It has been applied in surgery, anesthesia and in the ICU unit. It provides an objective, continuous, and direct measurement of oxygen in the adult, child and neonate and, in so doing, I certainly feel and I imagine most other physicians would feel as well, it has truly transformed the practice of medicine in that population. However, until now obstetricians had no way of measuring fetal oxygenation directly. They were forced to rely on indirect measures, such as the fetal heart rate.

We believe that the N-400, fetal oxygen saturation system, brings for the first time an objective, continuous and direct measurement -- and that is the important thing from my point of view, that it is objective and direct measurement of fetal oxygen to obstetrics.

What we needed to do, starting back in 1990, or so, was to extend the conventional oximetry technology to the laboring fetus. We had several special fetal issues to deal with. Most importantly, was that the fetal environment was extraordinarily difficult for that technology. We had a wet, unseen patient, with no accessible appendages -- no

hands, feet, fingers, ears or toes that we could wrap a band-aid around.

So, we had to develop a device that could be inserted through the cervical os and come to lie alongside the fetal face. This is such a sensor. The sensor is inserted during a vaginal exam, is inserted gently and allowed to advance until it comes to lie alongside the fetal face or temple. Most kids don't have beards so that is not a problem.

[Laughter]

It shines light into the fetal skin. It measures the color of the reflected light coming from the blood cells, and the monitor itself computes the saturation and displays it in real time. It is non-invasive to the fetus. It is, as you will hear later, quite easy to insert and comfortable for the mother. So, for the first time we are able to provide the obstetrician with a direct measurement.

The next problem we had was that we had to discover the threshold for clinical reassurance. That is, we had to define or discover the value above which we could, with assurance, say this patient or this child -- this fetus -- is adequately oxygenated, and below which there might be a risk of development of metabolic acidosis due to hypoxia.

We went about this in a methodological approach. We went to the literature and found studies from Brian

Richardson that indicated that 30 percent was a reasonable target. We did prospective animal studies which defined 30 percent as the critical threshold for the development of acidosis. I will explain that in a minute.

Then we did human studies, looking at the relationship between what is currently the gold standard for fetal assessment, scalp pH, and the value of saturation. That too indicated 30 percent.

This slide is from a prospective study of instrumented, near-term fetal lambs in non-laboring, unanesthetized ewes. The maternal ewe was exposed to graded hypoxia, and also the fetus was exposed to graded ischemia with common iliac artery occlusion.

On the vertical axis, on the left, you see the fetal saturation value from a catheter in the fetal lamb. In the vertical axis on the right, you see the value of the base excess from a blood gas drawn from that same catheter. At time zero the mother was made hypoxic; 30 or 40 minutes later the fetal oxygen saturation had fallen to a level below 30 percent, at which the lamb began to accumulate excess acid. As long as the saturation remained below 30 percent the acid continued to accumulate. When the saturation was allowed to rise above 30 percent, the lamb recovered the acid base status, and we found a critical threshold at 30 percent. That is, no animal above 30

percent accumulated acid; all animals below 30 percent accumulated acid at varying rates.

We repeated that -- this wasn't us; this was a perinatal research group. They repeated this same study with graded ischemia and found the same result.

We then went to Germany, where we did a multi-center clinical trial, looking at the relationship between scalp pH and saturation. In a series of 46 patients with non-reassuring fetal heart, they drew blood gases and compared the fetal scalp pH, shown on the vertical axis, to the fetal saturation, shown on the Y axis.

Using an ROC analysis, we determined that the critical threshold here seemed to be between 30 percent and 40 percent. We chose 30 percent for the clinical study. The reasons were quite simple. Animal studies had demonstrated that the critical threshold was, indeed, 30 percent, not 40 percent. We wanted clinically to reduce the number of false positives and, thereby, reduce the number of unnecessary interventions. We wanted to, therefore, maximize specificity and that way indicate choosing a threshold value on the left-hand side. In this case maximizing specificity would suggest a value of about 30 percent.

We also realized that this scalp pH versus saturation is inherently a conservative approach because 7.2

as a definition of fetal acidosis from scalp pH is quite conservative. Some people feel that the real threshold for concern ought to be lower and that, too, would suggest a lower threshold.

Finally, to be honest, there was a practical issue. We needed a value that had a line printed on the uterine activity charts, which is where we were going to display this thing, so that we could unequivocally in the protocol say you did reach the threshold or you did not reach the threshold. From a clinical use point of view, that turns out actually to be a pretty important issue.

For all those reasons, we used 30 percent as the threshold in the randomized controlled trial, and I am going to turn the podium over now to Dr. Tom Garite, who is not only the principal investigator of this study but actually the architect of the study.

Pivotal Study Design and Results

DR. GARITE:

Good morning, Dr. Blanco, distinguished members of the panel and distinguished interested members of the audience.

My name is Tom Garite. I am an obstetrician and specialist in maternal-fetal medicine. I am a professor and chairman of the Department of Obstetrics and Gynecology at the University of California, Irvine and, as David

mentioned, the principal investigator of this study.

I have no financial interest in Mallinckrodt, nor have I received any compensation from the company other than the support I received for the research to do the study and the compensation of my travel expenses to attend this meeting.

The design of the study that we will present today was as a result, as you might imagine, of extensive negotiation among the investigators and the sponsors to get a group of investigators to agree on a uniform protocol for interpretation and intervention for electronic fetal heart rate monitoring, as you all know, was no small feat. But we did eventually come to a uniform agreement which was presented and agreed upon by the Food and Drug Administration and, as previously mentioned, again presented and discussed a great deal at the advisory panel meeting of this agency in July of 1996.

The overall goal for this technology is to improve the accuracy and reliability of intrapartum fetal assessment. Perhaps the ideal study to do would be to design a study wherein we could demonstrate that this device improved fetal outcome. However, we concluded that this goal was unrealistic in that fetal damage due to intrapartum asphyxia is a rare event, and that the numbers required for such a study would be unapproachable.

Alternatively, we considered two other approaches. One would be a comparative study between fetal pulse oximetry and scalp pH. We rejected this for two reasons. First, it was just a physiologic surrogate which really did not test how the device performed in actual practice. Second, in reality fetal scalp pH is not something commonly done in the United States.

We ultimately chose to evaluate the endpoint of reduction of cesarian section for non-reassuring fetal status. This approach had the advantage of testing how the implementation of this device affected actual clinical behavior, and was a direct reflection of the hoped for improvement in the accuracy of fetal assessment by this new technology.

The study, then, was designed to test improvement in fetal assessment by measuring impact on physician behavior and neonatal outcome. Therefore, the study had three goals. First was to test to see if we could use fetal pulse oximetry, together with conventional fetal heart rate monitoring, to reduce the rate of cesarian section for the specific indication of non-reassuring fetal status. Next, was to be sure that continuing labor in the face of a non-reassuring heart rate pattern but a reassuring oxygen saturation was, indeed, safe. Finally, to demonstrate that the device itself was safe for mother and child.

The study we conducted was a prospective, randomized, controlled, unblinded interventional clinical trial comparing fetal assessment with electronic fetal heart rate monitoring alone versus electronic fetal heart rate monitoring backed up by fetal oxygen saturation monitoring. In both arms of the trial a study nurse was present from randomization until delivery to ensure protocol compliance and to enhance data collection.

To monitor study compliance and evaluate the accuracy of fetal heart rate interpretation and intervention, 100 percent of the cases and all of the fetal heart rate tracings were reviewed by an independent reviewer, Dr. Mike Nageotte, who did not participate as a clinical investigator. For the final analysis we used an intent-to-treat analysis with all patients included.

The study was conducted in three phases. The baseline phase was observational, with no pulse oximetry used. The purpose of this was to get an estimate of baseline clinical practice and to screen for sites willing and able to perform the study. As you can see, 472 patients were evaluated.

The second was the pilot phase. Here, randomization and data collection was practiced, as was the placement and use of the sensor, and for the sites to familiarize themselves with the use of the clinical

management protocol. Each site used a minimum of 15 patients and, as you can see, we had a total of 180 patients.

Finally, the randomized, controlled trial was begun. In this trial we approached a total of 4545 patients, of whom 2996 were consented. Ultimately, 1010 patients met entry criteria, were enrolled and randomized, 502 in the control and 508 in the test arms.

This slide shows all the study sites and their principal investigators. As you can see, these sties are geographically dispersed and well mixed between community and university hospitals, and those with and without teaching services -- nine sites in all.

Eligible patients included those in active labor, with a cephalic presentation at or below a minus 2 station, with ruptured membranes, and at or beyond 36 weeks of gestation, and also a singleton.

Patients were excluded if they were entered in any other intrapartum research study; if they were planning to have an elective cesarian section; had a placenta previa; any other need for immediate delivery, or an infection that precluded internal monitoring.

In general, patients were consented on admission but they were only actually enrolled if they developed a specifically defined abnormal heart rate tracing. These

fetal heart rate entry criteria included mild to moderate non-reassuring fetal heart rate patterns defined to allow early enrollment of patients who were at risk for developing more severe and concerning fetal heart rate patterns later.

In general, patient management was driven by the pattern on the electronic fetal monitor. These patterns were categorized into one of three classes. All of these classes are shown in detail in the clinical report. Patients with a class 3 or ominous pattern were delivered immediately in both groups. Patients with class 2 or non-reassuring pattern, such as persistent, late or non-reassuring variable decelerations. In both groups non-operative corrective measures were applied at the discretion of the managing physician and nurse to try to correct the fetal heart rate pattern. If these measures were unsuccessful and a non-reassuring heart rate persisted, then management differed between the control and test groups. In the control groups the physicians used either accelerations, spontaneous or elicited, or scalp pH to rule out acidosis. If acidosis could not be ruled out and the pattern persisted, the patient was delivered.

In the pulse oximetry group the clinician used oxygen saturation. If the oxygen saturation was above 30 percent at any time between contractions the physician was reassured and labor was continued. If not, if it remained

below 30 percent, then the patient was managed or, if a signal could not be obtained, then the patient was managed as if she had a heart rate monitor alone, i.e., accelerations or scalp pH was used, and if we could not be reassured with those, the patient was delivered.

The remainder of the patients with class 1 reassuring heart rate patterns were allowed continuance of labor.

Evidence to support that this protocol was clear and reasonable is supported by the fact that only four patients in each group had a significant protocol violation as determined by the independent reviewer.

The next four slides provide the pre-randomization clinical characteristics in the control and test groups. In this slide you can see that there no difference in maternal age, in racial distribution, in parity, in source of funding, or in the frequency of previous cesarian section.

There were minimal differences in maternal and fetal risk factors between the groups. I apologize for going through these kind of quickly. The labor characteristics were also quite similar in the two groups, with the exception that the frequency of labor induction and its associated pre-induction prostaglandin ripening were more common in the pulse oximeter group.

Critical to establishing appropriate randomization

for this study is the observation that the frequency of the defined entry fetal heart rate patterns was virtually identical between the two groups. You can see that the specific type of heart rate patterns that allowed enrollment and randomization were virtually identical. Therefore, we concluded that the two groups were well matched and that there was no evidence of meaningful selection bias between the two groups.

We also wanted to assure ourselves that there was no evidence of investigator bias or clinical management bias. We addressed the issue of investigator bias in two ways. First, management of two groups was reviewed by the independent reviewer for protocol violation, as I previously mentioned, with four significant violations in each group. Including or excluding these eight patients had no impact on any conclusion in the analysis.

Secondly, we examined the pattern and frequency of labor interventions and fetal evaluations between the two groups. Remember that both groups with a non-reassuring pattern were allowed standard labor interventions before proceeding to trying to reassure yourself, and you can see that things like oxygen administration, repositioning, etc. were quite similar between the groups, with the only difference being a slightly increased frequency of need for correction of hypotension in the pulse oximeter group.

Similarly, though not shown on this slide, and it is available in your clinical report, the frequency of both the most severely abnormal fetal heart rate pattern and the specific types of pattern, which led to the definition of a non-reassuring or ominous pattern and led to intervention, were also virtually identical between the two groups. So, there was an equal frequency of the worst fetal heart rate pattern in the groups. We concluded, therefore, that there was no evidence of investigator or management bias between the two groups.

The primary results of the study are shown on this summary slide. We found that the overall distribution of the route of delivery was similar between the two groups. As you can see, spontaneous vaginal delivery -- similar; assisted vaginal delivery -- similar; and the overall cesarian section rates of 26 and 29 percent were not statistically difficult. However, the indications for cesarian section were substantially altered. The rate of cesarian section performed for non-reassuring fetal status was reduced from 10.2 percent to 4.5 percent, more than a 50 percent reduction. This was the outcome for which the study was designed.

A logistic regression analysis demonstrated that a strong independent effect of pulse oximetry test group assignment resulted in this decreased risk for non-

reassuring fetal status. Unexpectedly and surprisingly, the C-section rate for dystocia increased to offset the reduction for C-section for non-reassuring fetal status.

Before discussing this dystocia issue, I would like to first discuss the reasons for the reduction for non-reassuring fetal status and the safety issues for mother and baby.

We were able to demonstrate that continuation of labor during periods of non-reassuring fetal heart rate but with reassuring fetal pulse oximetry was safe for the baby. This slide compares the immediate neonatal condition between the two groups, and shows that the reduction of C-section performed for non-reassuring fetal status was achieved without increase in adverse outcome.

There were five deaths. Two in each group were for complex congenital cardiac malformations. The third death in the test group is detailed in the clinical report. This baby's demise appeared to result from a delayed appreciation of attention pneumothorax, recognized about one or two hours post-natally, which resulted in severe metabolic acidosis. The baby had a normal 5-minute Apgar and borderline cord pH and went to the newborn nursery.

There were no statistically significant differences between the groups in the frequency of low Apgar scores, low cord pH, or base excess in the cord, or in need

for resuscitation. However, note that all of the neonates with extremely low cord arterial base excess are in the fetal monitor group, as are two-thirds of the low five-minute Apgar scores.

There were no significant differences in maternal outcome between the two groups either. Specifically, there is no difference in intrapartum fever or in postpartum fever or postpartum endometritis.

Thus, we conclude that both the use of the fetal oximetry sensor itself, as well as the management protocol tested in the study, is safe for mother and child.

This slide is very complex but very important, this and the next slide, and let me try to explain it as best I can. It is important to take time to describe we were able to reduce the cesarian section for non-reassuring fetal status without causing increased injury to the baby.

In this study, reduction of cesarian section for non-reassuring fetal status is a behavioral surrogate for improved accuracy of fetal assessment. Another method of evaluating accuracy of fetal assessment is to examine the degree of agreement between the physician's choice for operative intervention for non-reassuring fetal status and the actual immediate newborn condition. If we have provided a method of improved assessment for the clinician, then we should see an improvement in matching between the decision

to proceed with or avoid operative intervention and the actual immediate neonatal condition.

As previously pointed out, too often we perform an urgent cesarian section for concern over fetal oxygenation only to deliver an extremely vigorous and well oxygenated baby. Thus, the real hope for pulse oximetry is that we will be able to avoid such unnecessary operative intervention without missing babies who would really benefit from immediate delivery.

The most direct way to examine this agreement between behavior and immediate neonatal condition is to construct a series of paired 2 X 2 tables, one for the control group and one for the test group, comparing operative delivery or continued expectant management and actual depression versus no depression.

As you can see, as you saw on the previous slide, the results are similar for immediate adverse condition. However, this slide shows that numerous neonatal descriptors of immediate condition, and the number of neonates in each group with that condition, and the sensitivity and specificity for fetal heart rate monitoring versus pulse oximetry for that device.

In each case shown here, and with nearly any threshold for pH or base excess chosen, the sensitivity and specificity of the decision for operative intervention

versus neonatal condition is better in the test group than in the control group. Here you see sensitivity for a low pH compared with fetal heart rate monitoring versus oximetry statistically improved, and specificity for fetal heart rate monitoring versus oximetry statistically improved in the oximetry group. The final column gives the significant value of the difference in sensitivity and specificity given by the Mantel-Haenzel test for homogeneity of odds ratios.

I want to point out that although the numerical differences in the specificity may not appear to be as impressive as the statistical significance, it is important to point out that, for example, for pH the 78 percent specificity represents a false-positive rate of 22 percent for fetal monitoring versus a false-positive rate of only 14 percent for pulse oximetry. Thus, the numerical difference and the statistical significance are both not only statistically significant but clinical relevant.

We, therefore, draw the following conclusions: This is a large, well executed, multi-center randomized, controlled trial, with a high degree of study compliance. The addition of fetal oximetry monitoring to conventional fetal heart rate monitoring improves the accuracy of fetal assessment and permits safe reduction in the number of cesarean sections performed for the specific indication of non-reassuring fetal status without causing injury to mother

or child.

On a personal note, I just want to state how gratifying it has been to be involved in a large, well-conducted, randomized, controlled trial of a diagnostic device, using an intervention protocol, before the device was introduced into clinical practice.

Thank you for the opportunity to present this study. Now we need to examine and understand the reason why the overall number of cesarean sections because of the increase of cesarean sections for dystocia in the study group occurred, and my colleague, Dr. Rich Porreco, will present this study analysis.

Cesarean Section for Dystocia and Clinical Utility

DR. PORRECO: Thank you, Dr. Garite. My name is Rich Porrecto. I am a perinatologist in Denver, and I was the principal investigator at Presbyterian St. Luke's Medical Center for this trial. I have no financial relationship to Mallinckrodt, although I am told they will cover my expenses to come here, to Gaithersburg.

You have seen this slide before. This is the primary outcome slide that Dr. Garite showed you, showing that the overall cesarean birth rate was identical between the control and test groups, largely as a result of the fact that dystocia was increased among the test patients compared to the control group.

This study, as the panel may be reminded, was not designed to investigate the incidence of dystocia and, therefore, I think our retrospective analysis of these observations have to be qualified. However, the observation was compelling enough that I think all the investigators felt that we should carefully review this data retrospectively and try to come to some reasonable conclusions.

We considered four possibilities for these observations: One, unbalanced patient risk factors, despite the randomized methodology, might account for it. Mislabeling of dystocia due to bias of the investigators, that is, investigators rooting for the device might mislabel their true indication for cesarean section as dystocia rather than fetal distress. Thirdly, did the sensor use itself somehow manage to slow labor? Finally, was the finding of reassuring fetal oximetry information, permitting the continuation and the natural evolution of labor unmasking some underlying risk of dystocia?

Let me try to flesh out some of these considerations. As Dr. Garite has pointed out, the study entry characteristics were well balanced. The increase in inductions and prostaglandin use among study patients washed out with a logistic regression analysis. Also, the same analysis showed that C-section for dystocia was an

independent effect of being assigned to the test group.

On this slide, we considered secondly whether there was mislabeling of dystocia due to investigator bias. In a retrospective, blinded analysis of partograms defined dystocia, as you see noted here -- arrest of dilatation in the active phase of labor for more than three hours, arrest of descent in the second stage for more than two hours, or failed induction, that is, oxytocin administration for more than twelve hours in the presence of ruptured membranes was looked at.

On this slide you see that retrospectively assigned this definition of dystocia, both 90 percent of the control patients and 90 percent of the test patients who were sectioned for dystocia truly had dystocia, and those that did not were represented equally in either group. So, that is evidence of no mislabeling by the investigators.

Additionally, there was this concern that the investigators, again rooting for the device, might let fetuses with true distress languish somewhat and section them belatedly for dystocia. Looking at patients in the test group who were sectioned for dystocia, you can see that occurrence of depressed fetuses was uncommonly seen as opposed to those in the test group sections for non-reassuring fetal status. Again, corroborative evidence that there was no mislabeling due to investigator bias.

On this slide, the third concept was whether the use of the sensor itself slowed labor. In this Kaplan-Meier analysis of time to delivery, you can see that the curves are superimposable. Indeed, the test group had slightly faster labors and, if there was any slowing by the device, it should occur irrespective of the mode of delivery. These Kaplan-Meier curves show no slowing irrespective of the mode of delivery.

Lastly then, the issue of whether improved knowledge of fetal status would not only explain the decreased occurrence of cesarean section for fetal distress for non-reassuring fetal status, but also explain the increased occurrence of cesarean birth for dystocia. You have already seen that patients who were delivered for dystocia actually did have dystocia, and in patients with non-reassuring heart rate traces, reassuring oxygen information permitted the natural evolution of labor, continuation of labor, potentially unmasking underlying risk of dystocia. And, if this is the case, we should see an increased rate of these class 2 fetal heart rate patterns, the ones that require some intervention on behalf of the investigators.

This is exactly what we have seen. You can see that in patients who were sectioned for dystocia, in the test group, the class 2 non-reassuring patterns, especially

variable decelerations, are largely segregated here, in this group, much more so than the fetal heart rate control group alone. This, in balance, was seen only among patients who were sectioned for dystocia, not among other cesarean birth indications.

So in summary, we would suggest to you that our retrospective analysis of dystocia and non-reassuring heart rate traces -- that patients in the control group with non-reassuring heart rate traces are delivered by cesarean section for presumed fetal distress, syphoned off, if you will, and sometimes inappropriately, and delivered by cesarean section for that indication, whereas, in the test group the reassuring information of fetal oximetry permits labor to continue, to evolve naturally, unmasking, if you will, their underlying risk for dystocia. Therefore, the non-reassuring fetal heart rate that formulates our inclusion criteria, especially variable decelerations, may be an inherent marker for dystocia.

Now, this is not a new finding. The early studies of fetal heart rate traces, from the '70s by Havercam, showed an increased occurrence of cesarean birth for fetal distress and for dystocia. And, we know that positions of the fetal vertex, especially persistent ocipitoposterior positions, are associated also with severe variable deceleration and also associate strongly with cesarean birth

for dystocia.

So in summary, abnormal fetal heart rate patterns are common, and even with expert interpretation and lots of experience we find some built-in ambiguity. This ambiguity causes a lot of "medicalization" in a birth environment. Nurses and physicians look at the monitor strip, wrinkle their brow, cause a lot of anxiety in the birth mother, they turn her on her side, turn the IV up, put oxygen on, and the whole event becomes "medicalized." I think the addition of oxygen information can objectively and unambiguously tell that family that their fetus is well, and remove that "medicalization" from the birth scene.

Finally, intervention for the right indication at the right time is extremely valuable to these families. A calm and confident cesarean birth, when it is done in a program methodically for dystocia, is very difficult from one that may be done urgently, potentially under general anesthesia, with concern by the family about the well-being of their child, and we should not underestimate the value of being able to reassure these families that their fetus is well even if ultimately their underlying risk for dystocia is unmasked three or four hours later down the line.

Additional comments about the clinical utility of this device are going to be presented to you by Dr. Frank Boehm, and I will turn it over to Dr. Boehm.

Impact on Clinical Practice

DR. BOEHM: Good morning. My name is Frank Boehm. I am a Professor of Obstetrics and Gynecology at Vanderbilt Medical Center, and Director of Maternal-Fetal Medicine at Vanderbilt Hospital.

For the record, I have no financial interest in Mallinckrodt Company. Neither myself nor any of my immediate family own stock in the company. In addition, I have received no financial remuneration for this particular randomized study, however, my nurse's salary was paid for Mallinckrodt during the study period. I will receive travel expenses for this trip to make this presentation to the FDA panel.

I believe that the clinical significance of this new technology is in its ability to aid the healthcare provider in caring for laboring patients whose electronic fetal monitor tracing reveals non-reassuring fetal status. It will allow physicians to do the right thing for the right reason at the right time. It will allow us to reassure not only ourselves but our patients as well that while the fetal heart rate monitor may be somewhat confusing or not specific, the Nellcor pulse oximeter sensor indicates that the fetus is not hypoxic. A reassuring fetal oxygen saturation is reassuring not only to the physician but also to the patient. It acts as an adjunct to electronic fetal

monitoring which may be somewhat confusing or non-specific, and fetal oxygen saturation of 30 percent or greater indicates that the fetus is not hypoxic.

Importantly, this device will help physicians and nurses in their continued endeavor to have women empower themselves in decision-making processes during labor. When physicians are responding only to electronic fetal monitor tracings, they take away some of the options that women have in making decisions. With the Nellcor device patients will be better able to more objectively understand the issues and risks to their fetus.

In addition, because of the ability to be more sensitive and specific, the Nellcor device will allow physicians to approach the need for cesarean section in a more intelligent fashion. In the past we, physicians, approached cesarean section in either an urgent manner or an elective manner. This increases some of the risks to patients during the surgical procedure. By being able to reassure ourselves that surgery can be done in a more relaxed and planned manner, a non-emergent procedure can, therefore, reduce not only anxiety but, more importantly, can reduce risks to patients undergoing cesarean section.

Doctors and nurses are under tremendous pressures in taking care of the laboring patient. One of these pressures is to properly interpret electronic fetal monitor

tracings so as to make appropriate decisions in how to manage labor, as well as to explain to patients and their families the status of the unborn child. However, because of many ambiguities of electronic fetal monitor tracings, we need a mechanism to allow for objective data that will remove these ambiguities in electronic fetal monitor interpretation. The fetal pulse oximeter is a device which will give healthcare providers and patients that needed objective data.

In summary, I believe the Nellcor fetal pulse oximeter will have a significant impact on the field of obstetrics. Particularly, the approximately 30 percent of patients with non-reassuring fetal heart rate patterns will have more objective data that will allow clinicians to ascertain whether, in fact, the fetus needs to be delivered quickly or whether the patient can continue in the laboring process. This will have a significant impact on the cesarean section rate for fetal stress or distress, and will lead to more appropriate decision-making by all involved.

Now, to highlight these comments I would like to present one case from our institution at Vanderbilt. While each investigator had their own case, this is ours that I would like to share with the group. This is a private patient of mine, a 42-year old, gravida 2, para 1 at 38 and 6, 7 weeks. The patient underwent a low transverse cesarean

section for failure to progress at approximately 8 cm, with an occiput transverse position. The baby weighed 8 lbs. 9 oz. This was a delivery that I attended.

In the patient's second delivery the estimated fetal weight at term was 7.5 lbs. and the patient strongly desired a vaginal birth after cesarean section. Prenatally, the patient underwent an amnio for normal carrier type and was treated with Synthroid for hypothyroidism.

She was admitted to the hospital for an induction. The patient was 2 cm, 70 percent, minus 2 station, vertex. The fetal heart rate was 140 and reactive. There were no contractions. This was the fetal heart rate upon admission to the hospital. As you can see, the fetal heart rate is stable and reactive with these accelerations.

At 9:45, rupture of the membranes was performed. Clear fluid was noted, and the patient was now 3 cm, 50 pc and minus 1 station. At 10:45, an epidural was placed because of painful contractions. The patient now was 3-4 cm, more effaced and now engaged. This was the fetal heart rate at approximately this time, 10:45 in the morning, and you can see again the acceleration, moderate variability, and a normal fetal heart rate tracing, with uterine contractions occurring down here.

At one o'clock, the patient dropped her blood pressure slightly, had an increase in intravenous fluids and

the blood pressure improved, and she was making progress. This was the fetal heart rate tracing at the time, again a reassuring fetal heart rate pattern.

At 5:30, however, things changed. The fetal heart rate baseline went to 175 to 180. There were persistent late decelerations according to the nurses. The blood pressure was normal. The patient once again hit that magic 8 cm, full effacement, and was now plus 1 and left occiput transverse. A fetal scalp electrode was placed, and because of a mildly elevated temperature, ampicillin was started; oxygen was given and Pitocin was continued, and the patient was explained the process of randomization and the availability of the Nellcor sensor device.

This was the tracing at 5:30 when the discussions began and, as you can see, the heart rate is 180. There is minimal variability and there are these decelerations that were interpreted as late decelerations -- certainly, a quite non-reassuring fetal heart rate pattern.

At 6:30, the patient consented, was randomized fortunately to the sensor group, and her heart rate showed persistent late decelerations with an advancing tachycardia now, as high as 195 and, interestingly, the pulse oximeter reassured us with a 35 percent reading.

This was the initial heart rate tracing, and you can see the heart rate here has not really changed. There

is still considerable tachycardia, persistent decelerations after the peak of the contractions and minimal variability. At this particular point, the sensor is not reading appropriately here and the nurse has written down the pulse oximetry of 35 percent and 33 percent. We will get to the appropriate reading in a second.

This is immediately following, and you can see this tracing of a patient with a previous cesarean section still at 8 cm -- it was very intriguing to consider a cesarean section but because the pulse oximeter reading was in the 33 percent to 41 percent we continued the labor.

At seven o'clock, you can see that the heart rate was still up, minimal beat to beat, persistent lates, however, the pulse oximetry was in the reassuring range and the patient was now 9 cm and plus 1, with a temperature of 100.7.

At this point, the pulse oximeter is working appropriately to register onto the paper, and you can see that it is above 30 percent during this time. There are these continued decelerations. Again, the pulse oximeter reading is down here. I believe there is one point where it drops for a few minutes below 30 but the rest of the time it is above 30. The patient is allowed to continue her labor.

At 7:40, the patient was now complete, plus 2 and pushing, and again the pulse oximeter was in the 32 percent

to 40 percent range. This is that particular period. You can see the pulse oximeter is well above 30. The patient is pushing, and this is the fetal heart rate that we are obtaining with the fetal scalp electrode in place; minimal variability and decelerations.

Finally, at the end the scalp electrode is removed and delivery occurs. This is the last portion of the tracing prior to taking everything off. The pulse oximeter was in the reassuring above 30 range.

The outcome is seen on this slide, at 8:04. No forceps delivery. Apgar of this male child was 9 and 9, and the cord blood gases, artery and vein, you can see are a reassuring 7.20 and base deficit of minus 6.8 in the artery which I think is most reassuring.

At this time, I would like to introduce Nancy Townsend, clinical nurse specialist, who was the Vanderbilt Nellcor project research nurse. Thank you very much for your attention.

Nursing Perspective

MS. TOWNSEND: Good morning. My name is Nancy Townsend. I am an advance practice nurse at Vanderbilt Medical Center, in Nashville, Tennessee, and was the study coordinator for the fetal pulse oximetry research project at our institution.

For the record, I have no financial interest in

the Mallinckrodt Company. Neither I nor any of my family members own stock in the company. During the course of the research project, my salary and benefits package was entirely supported by Nellcor and Mallinckrodt. I am not being paid for this presentation, however, Mallinckrodt will reimburse my travel expenses.

Before I begin the formal part of my presentation, I would like to make a note about the case study which Dr. Boehm just presented. In the very beginning part of the case where the sensor was placed, I was the nurse who was present during that case. I handwrote the fetal oxygen saturation readings on the monitor tracing. We had adequate signal quality and that was an appropriate reading, however, it just was not tracing on the monitor because I had not plugged in at the back of the monitor the proper plug to allow it to trace, and I figured that out and plugged it in and that is why it was handwritten in the beginning. Again, we had adequate signal quality and it was an appropriate reading.

I have polled many nurses with experience in fetal oximetry, both in my own institution and around the country. The responses have been overwhelmingly positively from a nursing standpoint. There is no greater challenge to the perinatal nurse than coordinating a safe, satisfying birth experience for the child-bearing family. To provide a safe

birth experience, the priority in nursing care is to ensure that the mother and fetus are adequately oxygenated. In performing this duty, nurses face a similar dilemma as physicians in that standard electronic fetal heart rate monitoring is only an indirect means of assessing fetal oxygenation status.

Furthermore, since nurses have a tremendous impact on patient satisfaction during the labor and delivery experience, nurses must do everything within their power to act as advocates for their patients.

Within the context of nursing's key role in the birthing process, my belief is that the fetal oximeter is an important tool for nurses in providing the best possible outcome for families during childbirth in the frequent presence of a non-reassuring fetal heart rate tracing. The entire healthcare team and, thus, the childbearing family is reassured by certain measures of fetal well-being on an electronic fetal heart rate tracing, such as moderate baseline variability or accelerations above the baseline fetal heart rate.

Based on scientific evidence, nurses know that these signs are almost always indicative of an adequately oxygenated fetus. However, nurses are also well aware that in the presence of non-reassuring signs, such as fetal tachycardia or late decelerations, the evidence is non-

specific. In other words, a non-reassuring tracing may or may not indicate deterioration in fetal oxygenation status. Up until now, the only method of directly assessing fetal oxygenation has been fetal scalp blood sampling.

This process is uncomfortable and undignified for the patient, time consuming for the obstetrical staff, costly and, most importantly, invasive to the baby. When fetal status continues to be non-reassuring as assessed by fetal heart rate monitoring, the fetal scalp pH test must often be repeated several times. Furthermore, in the presence of a vaginal infection, laceration of the fetal scalp may potentially expose the fetus to harmful microorganisms.

The fetal oxygen saturation monitor is a non-invasive device that gives a clear and direct reading of fetal oxygenation status. The sensor is easy to place at different dilations, with no awkward positioning required for the mother. If the signal is lost, a simple readjustment restores the signal usually without a vaginal examination.

Patients are reassured by the presence of a comfortable, non-invasive device which gives clear and continuous information about their unborn child's oxygen status on a monitor that is easy to understand. A concise explanation about the technology and the data allows the

nurse to effectively communicate key information about fetal status and, thus, decrease patient anxiety. Objective information from the fetal pulse oximeter is helpful since the nurse can refocus the patient's attention to reassuring fetal oximetry data. Plus, since there is a specific number above which metabolic acidosis may be ruled out, clear-cut reassurance is available to both the patient and the nurse.

Information is important to both nurses and patients at every stage of labor. There is a clear link between a patient's feeling of control and with their satisfaction with the birth experience. It has also been suggested that with greater birth experience satisfaction, a woman is better able to mother her child. If the nurse is able to provide clear, concise information from the fetal pulse oximetry system, more information and ultimately more control are given to the patient. Information must be shared with families no matter what the situation. A new technology that is easy to use, non-invasive and provides reliable and objective information is, therefore, a very good thing.

Nurses favor fetal pulse oximetry for another major reason. When the fetal heart rate tracing is non-reassuring but fetal oximetry data is reassuring, as if often the case, the nurse is reassured. Thus, the patient is given every opportunity to have a vaginal delivery. This

reassurance is documented on the fetal heart rate strip and in the nursing notes, and can be clearly communicated to the physician. The nurse is then free to provide more direct labor support to the laboring mother and her family instead of focusing too much energy on the often ambiguous fetal heart rate tracing. This clear communication of fetal status to other members of the healthcare team, particularly to the physician, is another reason why nurses favor this new technology.

Because fetal heart rate tracing interpretation is subjective, it is not unusual for nurses and physicians to disagree when reviewing the same fetal monitor tracing. This disagreement increases the tension and stress among all those involved in the labor-delivery experience. Another advantage of the oximeter is that nurses, with a physician's order and with proper competency validation, may potentially place the sensor independently.

In summary, fetal pulse oximetry is easy to use. It is non-invasive to the fetus. It is comfortable for the mother, and it provides valuable, objective information that reassures both the childbearing family, especially the mother, and the obstetrical staff. For all these reasons, nurses like this technology. Most important, it is good for the patients whom we serve.

Next, I would like to introduce Ms. Lucy Woods.

Patient Perspective

MS. WOODS: Good morning. My name is Lucy Woods. I have no financial interest in the Mallinckrodt Company. I am not being paid for this presentation, although they are reimbursing me my travel expenses.

By the way, I am the patient in the case that Dr. Boehm discussed earlier. I did have a C-section with my first little boy and, along with having a very healthy big baby boy, I was also very uncomfortable for the first few weeks. I really couldn't be the kind of mom I wanted to be. It was uncomfortable holding him. The baby and I were both uncomfortable when he was trying to nurse. So, it was a few weeks down the road before I really felt that special bond because I think he sensed that I was not myself, and I think the C-section really made a difference in how quick we got comfortable with each other.

I know when I went into labor with my second baby boy, Seth, how much I wanted to deliver him, and I distinctly remember, I was lying there, watching the monitors and I thought that doesn't look right. Well, about the time I felt that my nurse looked at me and I said, "something's not right, is it?" And, she said, "well, I'm going to call Dr. Boehm." Well, he came in and he explained the situation. He told me the possibility that I could have another C-section and immediately I was just, like,

terrified. I didn't want another C-section. I wanted to be able to go home to my two-year old, take my baby home, you know, be able to pick them up, love them just like a mom ought to do.

Well, Dr. Boehm informed me of a study that Vanderbilt was doing at that time, and it was the pulse oximeter. Well, I said, "please call Nancy in; I would love to talk to her." Well, Nancy, the study nurse, came in and she explained what the pulse oximeter was. She explained how it worked, everything involved with it. Of course, my main question was would there be any harmful effects that the baby could have by attaching the sensor, or anything like that. Well, she reassured me. Dr. Boehm seemed very confident with the instrument and, after talking with both of them, I felt very confident in using the pulse oximeter.

There was no discomfort at all when it was placed on the baby's face. A few hours later I delivered a very healthy 7 lb. boy. I remember when Dr. Boehm first showed him to me, I saw tiny little red mark on his cheek. Well, by the time they brought him back to me the red mark was totally gone. You know, I thought, "wow, this is wonderful." Within an hour, I told my husband, I said, "I'm ready to get up." I said, "I feel great." And the nurse that was in my room, she said, "are you sure you can get up?" I said, "yes, I feel wonderful."

Well, I got to nurse the baby. He and I bonded immediately. I mean, I could hold him and love on him. When I went home, of course, my two-year old, he missed his mommy; he came running up and I got to hug him and hold him instead of saying, "oh, no, don't touch mommy." And, this just made all the difference in the world. I got to, you know, hug and love my two-year old. I got to nurse my baby, you know, and we were both comfortable doing it. From the very first time he nursed, everything went perfect, which was a definite change from the first time. It was just wonderful being able to go home and be the mom that I wanted to be for both my children, and I just hope -- I think this instrument is just a wonderful thing and if it saves anyone, any woman from having an unnecessary C-section it is well worth it.

Thank you.

Restatement of Proposed Indication for Use

MS. PAGE: I would like to recap the results presented here today. We have demonstrated that the use of the N-400 system with conventional fetal heart rate monitoring allows the safe continuation of labor during periods of non-reassuring fetal heart rate and reassuring FSpO2.

Use of FSpO2 improves the quality of fetal assessment and results in better matching of delivery

indication and immediate neonatal condition.

Finally, the improvement in fetal assessment results in a clinically meaningful 50 percent reduction in the rate of C-sections performed for non-reassuring fetal status even though, as we have seen, the overall rate of C-sections remains unchanged.

Furthermore, we believe that the results support our indication for use statement as previously presented. The system is to be used as an adjunct to fetal heart rate monitoring. It is to be used in a population of term infants with ruptured membranes who have a non-reassuring fetal heart rate pattern, and the purpose of the N-400 system is to improve the physician's ability to assess the fetal status.

In summary, we believe that the study we have discussed today does, indeed, constitute a valid scientifically sound study; that the results are clinically significant and, most importantly, we believe that we have demonstrated the safety and effectiveness of the N-400 Fetal Oxygen Saturation Monitoring System for its stated intended use.

This concludes our presentation. We thank you for your attention and we do welcome your questions at this time.

CHAIRMAN BLANCO: Thank you very much to the

company for the presentation. We have a few minutes left over in the schedule and I will see if any of the panel members have any questions that they would like to direct to any of the representatives that presented at this time. Diony?

MS. YOUNG: Thank you. I am Diony Young. It has been very interesting listening to all of the information about the study. I want to talk about the real world. First of all, the study assumes that all women are put on an electronic fetal monitor. That is not the case, though the majority are in this country. No mention has been made of osculation, and the use of osculation with the use of this device.

My first question would be if a non-reassuring heart rate pattern is found on osculation, what is the sequence of obstetrical interventions? Electronic fetal monitoring, external or internal fetal scalp sampling, then followed by oximetry? That is my first question.

My second question is in the study it was mentioned that all the women were attended by a nurse throughout the study. In the real world, with nursing cutbacks, the situation I think is very difficult in most hospitals and few women are lucky enough to have a nurse with them, one-on-one, throughout their labor. So, does this device require one-on-one staff attendants at the

mother's bedside throughout her labor? So, could I have answers to those questions, please?

DR. GARITE: Yes, ma'am. I think your question is important but I think both questions can be answered simply, and then I will get to the details, with one statement and that is, this device is only intended to be used at present in patients who already have evolved to the point where they have a sufficiently non-reassuring fetal heart rate tracing that the clinician needs further information to assure himself or herself that intervention is not required. Therefore, in the osculation setting we, at our hospital, for a number of years had a free-standing birthing center where our midwives used osculation for the primary means of fetal surveillance. But we, as I believe virtually everyone on this country, in the presence of a non-reassuring osculation backed it up with an electronic monitor. So, you go through the same sequence. If the electronic monitor is non-reassuring then, depending on your mode of practice, you use either accelerations or scalp pH to back that up. If you can't be reassured at that point, you end up with a cesarean section, but this device would then fall into place in that sequence, allowing further more accurate fetal assessment.

In the monitor protocol, the research nurse was not the patient nurse. Okay? We weren't trying to create

an unreal situation. The research nurse was there to monitor protocol compliance and the patient had a clinical nurse. But, nonetheless, your question is cogent, and the reality is again answered by the same question, you don't have a one-on-one nurse in real life. I wish we did, but we don't, especially in my institution. We can't afford it. But when we do have a patient who has a sufficiently concerning fetal heart rate pattern that you are to the point where you might be intervening for non-reassuring fetal status by either a section or a forceps, at that time most of the time you do have a nurse that is pretty much with the patient.

So, that is where we are in the evolution. We are not there at the beginning or in the normal labor, or anything like that. This device is intended to be used when you are at the point where you need further information, and our best estimate is that it is somewhere around 25 percent of patients in this country.

MS. YOUNG: Okay. One more quick question, and it relates to maternal position. This device is an adjunct so the woman is actually hooked up to a lot of different things. I sort of have this picture of her flat on her back which, in and of itself, can cause fetal distress. She has a lot of wires coming out of her body. You know, how long is she going to stay there, in that position? I understand

that there is a problem if she actually moves. Excessive movement is mentioned in the materials. I don't know quite what excessive movement is but presumably she can't get up and ambulate which also itself may, you know, increase the fetal well-being, if she is allowed to do that because changes in maternal position can definitely have an effect on fetal well-being. So, is she flat on her back for many hours, hooked up to all of these things?

DR. GARITE: There is no need to be flat on your back to have this device. Mothers labor on their sides when they have non-reassuring fetal heart rate patterns, and with this device they labor on their sides.

Yes, it precludes ambulation. I am not aware of data that suggests that ambulation improves fetal oxygenation. Being on their side or their back does. But, again, I will go back to my statement on my previous two questions, this isn't intended for use on the average laboring patient; it is intended to use when you get to the point where you are so concerned about fetal status that you are now being interventive. In reality, instead of a patient going urgently for cesarean section, the intent is that a woman who can continue laboring at least on her side and, you know, in the spectrum of ambulation, laboring on your side and having a knife on your abdomen, I would choose laboring on my side. But that is just a little editorial

comment.

CHAIRMAN BLANCO: Let's try to be succinct. We are still in the information stage so other questions?

DR. SHARTS-HOPKO: Yes, I understand that this would have been done for control purposes in the study but it is sort of reinforced in all the training materials, is this device intended only when the fetus is in a vertex presentation?

DR. GARITE: That is correct.

DR. DIAMOND: I had a question about the protocol itself. The patients were consented into the study at what point?

DR. GARITE: There were three different phases. In many, and most of the institutions, if possible a brochure was distributed in the prenatal period to describe the study. That was not required. On admission, whenever possible, all patients were consented whether they were eligible for enrollment by the fetal heart rate pattern or not. In other words, if they had a vertex, if they were at term, in labor, they were consented but they were not enrolled or randomized until they met all the eligibility requirements, including abnormal heart rate pattern. Some patients were not enrolled on admission; they were consented at the last point as well.

DR. DIAMOND: Do you have the information on the

breakdown of patients between the latter two categories that you just described?

DR. GARITE: No, I don't have that available.

DR. DIAMOND: Okay. The ominous heart rate pattern, the class 3 -- maybe I missed it but I didn't see where that data was -- how many of the patients in each group had that, or how many patients who were consented were then not enrolled because they developed that, precluding time for their randomization to one group or the other? Do you have any of that data?

DR. GARITE: Yes, we do.

DR. SWEDLOW: This is Dave Swedlow. My recollection is that there were 15 or 16 ominous patterns in both groups, no difference between the two. Could you repeat the first question?

DR. GARITE: Actually, the study criteria, in essence, excluded some of those patients. If they developed an ominous pattern before randomization, they weren't eligible for randomization because requiring immediate delivery was an ineligible criterion. I know that could inherently bias things, but you can't randomize someone --

DR. DIAMOND: Sure. That is why I was asking. As you indicated, that could potentially bias --

DR. GARITE: They couldn't even be enrolled if they developed that pattern as their first pattern.

DR. DIAMOND: But they could already have been consented potentially.

DR. GARITE: They could have been consented but they would not have been randomized. Those ominous patterns could only be included in patients who were already randomized and already either in the monitor or control group. That could not have been an entry criterion.

DR. DIAMOND: Yes, but there could have been some that were consented that developed that, which precluded just what you described.

DR. GARITE: Absolutely.

DR. DIAMOND: Did that happen once? Did that happen in a hundred patients?

DR. GARITE: I have no idea.

DR. DIAMOND: You don't have that information?

CHAIRMAN BLANCO: Okay. Subir?

DR. ROY: I was trying to understand better Dr. Porreco's presentation. In slide 38 we have increased rate of non-reassuring fetal heart rate seen only in test patients sectioned for dystocia, and it is broken down into class 2 variable decelerations, both of which occurred more frequently in the test group. Then, in the next slide, it is concluding that test group reassuring fetal oxygen permits labor to continue unmasking dystocia, therefore, non-reassuring FHR is a marker for dystocia. I mean, did

these people have a true identification of fetal distress or not?

DR. PORRECO: No. Well, they met inclusion criteria to be randomized and that is what we are suggesting. When we go back and look at our database and observe this retrospectively, the increased occurrence of dystocia. The fourth possibility is that these patients unwittingly were selected not only to have an increased risk of fetal distress or non-reassuring patterns by their inclusion but unwittingly we selected a group, we believe, that had an increased underlying risk of dystocia, and being randomized to the sensor group permits the evolution of their labor and unmasks, if you will, that increased predisposition to dystocia. In the absence of the monitor, those patients would have been syphoned off and sectioned inappropriately in some cases for fetal distress had they been randomized to the control group.

DR. ROY: So the reason for the cesarean section in the control group would have been for these tracing patterns.

DR. PORRECO: Correct.

DR. ROY: And for the monitored group for dystocia.

DR. PORRECO: The sensor group for dystocia.

DR. ROY: But they also had the tracing

abnormalities?

DR. PORRECO: Yes.

DR. ROY: I guess that is what I am getting that.

DR. PORRECO: Yes, and their labor, instead of being truncated, if you will, continued because the reassuring improved assessment allowed it to proceed and then ultimately if they, indeed, were in that group of an underlying risk of dystocia, it became manifest two, three or four hours later. That is our interpretation of the occurrence or the observation that these patients had a higher rate of cesarean birth for dystocia.

DR. ROY: Are we saying that that is a good thing?

DR. PORRECO: Are we saying that is a good thing?

DR. ROY: Yes.

DR. PORRECO: We are saying that improved fetal assessment is a good thing, doing the right thing at the right time for the right reason. That is, knowing that patients who are intervened upon sometimes in urgent status by cesarean birth is appropriate only when, indeed, the fetus requires that kind of urgent intervention. The fact that they may have an underlying increased risk for dystocia, such that cesarean birth down the line is necessary for that indication, in a different program setting is still appropriate. I mean, that is a good thing.

CHAIRMAN BLANCO: Let me go ahead. We need to

keep going; the panel has a lot of other questions. Jay?

DR. IAMS: I just want to keep going on that same theme here, Dr. Porreco. Sooner or later there would have to be, if I am understanding you correctly, a decline in the number of cesarean sections if this technology were applied to a large population. I don't quite figure out how the C-section rate can stay the same if what you are saying is that your monitor identifies a group of women who may be at increased risk for dystocia, as well as for fetal compromise.

DR. PORRECO: Our inclusion criteria --

DR. IAMS: The inclusion criteria. Then, once that additional technology is in place, the fetal pulse oximeter should decrease the number of cesareans performed for non-reassuring fetal status, but that you are already operating on a group that has an increased risk of dystocia. We know that if you let labor that is a little dysfunctional go on -- at least, we think we know from the Alabama data and other places, that if you give women a little more time with a slow labor they may reduce their section rate there also. So, somehow or other, I am stumped on the notion that the C-section rate isn't going to change; we are just going to know who needs what. Shouldn't it ultimately go down? If you allow labor to progress safely we should see a reduced number of false diagnoses of dystocia plus fetal

intolerance to labor, and we should see a reduced number of sections for fetal compromise, no matter how you define it. So, is it just simply a matter of the N here? We just need to have --

DR. PORRECO: Yes --

DR. IAMS: -- ten thousand women and then we will see that? Is that what you are saying?

DR. PORRECO: Yes, and also the fact that if it was dystocia that we were after, as you suggest, we would need other information -- how much uterine activity were these women subjected to? What were the positions of the vertex in patients who weren't progressing? I think in our ability to look at our database -- since that wasn't what we were after, I think if one were after that, that is the kind of information that would have to be at hand to prove what you have just suggested.

CHAIRMAN BLANCO: We are starting to kind of get into a discussion and we really need to get the FDA presentation in before we do that. So, are any other questions of fact that we can either leave with the company to try to get to us by the time we start discussion, and so forth? And, let's try to do that quickly because we are now running behind instead of running ahead. Machelle first and then Dr. D'Agostino.

DR. ALLEN: I actually have a number of fairly

minor questions. I apologize for the number of questions and I hope they are simple to answer.

In our reading material, in volume 1 on page 10, talking about the accuracy of the monitor, they say a true fetal pO saturation of 30 percent -- 67 percent of the SpO2 readings can be expected to fall between 25 percent and 34 percent. I was wondering were you comfortable with the remaining 33 percent that are not accurate?

CHAIRMAN BLANCO: I think that is kind of part of the discussion, one of the questions that we are going to be addressing. If there is something that you need to know that they can look up and give us back before we start the discussion --

DR. ALLEN: I am just want to go right through them and see if they are appropriate questions or not. I wanted to know of the ten patients where we had difficulty in placing the monitor, any idea what caused the difficulty?

DR. GARITE: The most common reason was the vernix. Vernix is the one thing -- a really thick vernix -- that interferes with this. Some patients, however, with advanced dilation or low station --

DR. ALLEN: You just can't get it in?

DR. GARITE: -- also will have difficulty in getting it in, just like an intrauterine pressure catheter.

DR. ALLEN: On page 17 there is a referral that

there might be an interaction between placing epidurals at less than 5 cm along with the monitor. Is there a real interaction?

DR. GARITE: I will give you my best answer. Since the vast majority of patients had epidurals, what happens in the patients who got epidurals at greater than 5 cm, which is the minority, is that your N gets so small that you just may not have a substantial size. There is not enough data there to conclude in the other arm that there really is a difference or not.

DR. ALLEN: And then with the breaches, is that just because they were excluded so you have no data to support using this with breaches?

DR. GARITE: Well, one we didn't include breach as an inclusion criterion and there is really even internationally minimal data on malpresentations. Now, you may have some -- I know there is some.

CHAIRMAN BLANCO: Well, let's remember that the indication was to lower cesarean section in vertex with non-reassuring fetal heart rate patterns. So, the breach is really not an issue.

DR. ALLEN: Okay. Then, just philosophically, are you comfortable with non-reassuring fetal heart rate tracings being a surrogate marker for eventual dystocia?

DR. GARITE: I think we should be very careful how

far we go with this conclusion.

CHAIRMAN BLANCO: Let's leave that. That is really a discussion question, not a point of fact. Dr. D'Agostino?

DR. D'AGOSTINO: Let me ask and maybe they can respond quickly, but it probably would be more appropriate to respond later, after the break or something, the statistical analysis is extremely complex and, being a clinical trial even though open-label and so forth, and unblind once the randomization was done, it still is randomized and I guess one of the analysis techniques that one could have done was to look at overall analysis, like the Fisher exact test or something, very simply chi square or what-have-you, and then, after you have done that, instead of building a big logistic regression model, look to see what happens in subsets.

I guess my logic is that I would really worry about subsets in the sense of do you think that you have identified some groups where the procedure doesn't work, the monitor doesn't work? You mentioned site 3, for example, but then there is the obesity and the hypotensive. I think I would like some assurance, and maybe the panel also, is that even though you have identified all these variables that, in fact, you have no reason to think the procedure is going to not work in those subsets. Maybe you could get

that for us later.

Also, with regard to this dystocia question, let me just throw out an idea that would give some comfort to me and give me some understanding, if you have the monitor added to the monitoring, can you identify individuals that, without the new monitoring, would have gotten a C-section for the non-reassurance and then see what happens to those individuals? You may have said that but it is not clear. It would be very interesting to say where are the dystocia cases coming from.

DR. GARITE: I can answer that last question pretty quickly. It is not the exact same patients who had non-reassuring fetal heart rate patterns that ultimately developed dystocia. I mean, you heard from one that didn't. There are a lot of examples of those. It is a population effect; it is not the exact same patient. So, like I said, I think we need to be careful where we go with our ultimate conclusion.

DR. D'AGOSTINO: Then lastly, again just to think about it, in slide 27 you have 108 individuals versus 78 individuals. It is not completely clear to me where the 108 and 78 are coming from.

DR. GARITE: I will answer that real quickly. Those are the patients who had either operative vaginal delivery or operative cesarean section for the specific

individual of non-reassuring fetal status in each group.

DR. D'AGOSTINO: It would be interesting to tie them back to the rates that you give when you are looking at your efficacy analysis because they are not the same -- there is an overlap but not exactly the same.

DR. GARITE: I think you are confusing C-section and operative vaginal delivery. If you add the two of them together, they should add up. If they don't, we will check it.

CHAIRMAN BLANCO: Any other questions of fact over on this side? Dr. O'Sullivan?

DR. O'SULLIVAN: Tom, can you tell me how many patients actually had pO2's less than 30 during the monitoring process with the device?

DR. GARITE: Persistently less than 30?

DR. O'SULLIVAN: That that was what made you decide to do the cesarean section.

DR. GARITE: Right, how many actually had that and how many had no signal -- I will have to break it down. So, if you will allow us --

CHAIRMAN BLANCO: We will go ahead and maybe after lunch you can give us the answer.

DR. GARITE: Yes.

DR. CHATMAN: Dr. Garite, the epidural rate in these institutions generally is 95 percent and, if it is

not, how that might affect the data, if it does or if it could. I would like to know, secondly, how you arrived at the definition for dystocia because, as you know, there are other criteria that people use for the definition of dystocia.

DR. GARITE: We will check. What you really want to know though is, is the epidural rate that high in nulliparous patients, in patients who meet the same criteria who are not study patients because epidurals are clearly high in nullips and mulips so you can't take the hospital's gross rate to compare. So, I will have to get that for you.

I can answer the second question though, if you can repeat it again. I am sorry.

DR. CHATMAN: Just how you arrived at the definition of dystocia.

DR. GARITE: The definition of dystocia was solely based on partogram definitions. We did not prospectively know that dystocia was going to be a problem so we didn't include data on pressure catheters, etc., etc. So, we had to take some arbitrary retrospective definition purely based on labor progress, and it is arbitrary.

DR. CHATMAN: Okay.

CHAIRMAN BLANCO: Mike?

DR. DIAMOND: The first question is a little bit like the one that was asked. As I understood the protocol,

for those patients randomized to the test group if the pO2 was below 30, that is when they got evaluation for accelerations and scalp pH. How many patients actually had that testing done and, therefore, did not end up with a cesarean section based on the pO2?

DR. GARITE: Well, I can tell you the scalp pH. It was 15. It was about 15 in each group.

DR. DIAMOND: And did not end up with cesarean section because of that?

DR. GARITE: No, not necessarily. That is how many were evaluated. Because, you know, what you have is a dynamic problem. Sometimes the SpO2 falls below 30 percent, you revert to the heart rate, you have accelerations or normal scalp pH, and now your oximetry is normal. Or, the same thing happens with the heart rate, it goes back and forth.

CHAIRMAN BLANCO: But he is asking how many had it and what the result was. So, if you can get that data, after lunch we will expect that data.

DR. DIAMOND: The point is that the device is being used for that purpose. Was that information helpful? The second question is, based on the pilot data that you collected from other sources, what was the power calculation that you performed? What was the difference you expected between the groups and how did that turn out? How did you

make your calculations?

DR. GARITE: Well, the calculation was, indeed, based on the pilot study. We determined an overall rate of cesarean section for non-reassuring fetal status, which was --

DR. SWEDLOW: We expected a rate of 10-12 percent and we wanted a 50 percent reduction.

DR. GARITE: And we calculated 1000 patients, and the numbers were right on the button.

CHAIRMAN BLANCO: Dr. Eglinton?

DR. EGLINTON: Do you have your statistician here and your database on disc? Can you do another regression analysis here today?

[Dr. Garite nods in agreement]

CHAIRMAN BLANCO: I think we are going to go ahead and have a break. We are going to have a five-minute break. So, that is all we are going to get so we can get back on track. Thank you.

[Brief recess]

CHAIRMAN BLANCO: Let's get back and convene the panel again, please. We want to try and keep on time, and we are going to shorten lunch so that we make sure that we have enough time for the discussion agenda. Let's go ahead and get started.

Preclinical Aspects

MS. DAWS-KOPP: Good morning, ladies and gentlemen, distinguished panel members and guests. I am Kathy Daws-Kopp, the lead reviewer for FDA on this PMA. I have been working with this device since the IDE stage, which started over four years ago, and I am here to give you a brief overview of the review process that we have gone through on the preclinical portions of the PMA.

First, I would like to acknowledge the review team. As you can see, a number of people have been involved in the review of this PMA application. In addition to the basics of clinical and statistical portions that you are most familiar with, our review addressed engineering, materials safety, animal data, optics, manufacturing, human factors, sterilization and patient labeling.

In my presentation, I am going to focus on what we have looked at in the course of our preclinical review. Then I will outline a couple of ongoing issues that we are still working on with the company to resolve.

As Mr. Pollard mentioned in his opening remarks, this PMA was submitted as a modular PMA, where the company is allowed to submit portions of the information required for a PMA ahead of time. In this case, much of the preclinical information was submitted by the company before their clinical data was ready to be submitted.

In this slide, I have listed the modules that are "accepted and closed," a term we use with modular submissions to indicate that the issues addressed within the module have been addressed to our satisfaction. Most of the modules listed here were "accepted and closed" prior to the submission of the formal PMA.

I will briefly go through the list: General information gave us the basic administrative information required for a PMA.

Device characteristics was a detailed device description, how it works, the principles of operation, etc.

Pulse Simulator II describes a test tool that the company developed that uses recorded oxygen saturation information to verify and validate device modifications.

Software covers the software information, including the software hazard analysis, performance requirements, specifications, design and verification and validation information.

Biocompatibility provided information about the safety of the materials used, including test data as necessary.

Sterilization provided the sterilization methods, validation, etc.

Reports and other information provided a comprehensive literature search and analysis.

The PMA was officially submitted in September, and there were still some preclinical review issues outstanding at that time. These were rolled into the PMA. Since September, some of the issues have been resolved. The three items listed here are the only remaining issues for the preclinical review. I will briefly explain each of them.

Manufacturing has not been completely resolved because we have not yet conducted our inspection of the manufacturing facilities, a requirement for all PMAs. However, we have reviewed the documentation that was submitted and did not find any problems.

The product safety module addressed issues such as optical, thermal and electrical safety. A couple of questions remain in this area.

The animal, bench and non-IDE testing covered preclinical and clinical studies other than the pivotal trial discussed here today. This is where the concept of device accuracy is first addressed in the PMA submission.

I will now summarize the status of these last two items. In regard to product safety, one of our purposes has been to evaluate the information provided in regard to the thermal and optical safety of the sensor.

Because the optical and thermal output of the sensor is so low, we do not expect this to pose a problem. Additionally, very few adverse events that can be

specifically linked to the device, such as erythema, were recorded during the pivotal clinical study. However, we are still working with the company to close the gaps on the scientific basis to corroborate the clinical experience.

Human factors is intended to look at the usability of the device, that is, to evaluate the ergonomics or how user-friendly the system is. Occasionally, this type of review can turn up troubling juxtaposition of controls or sequences of actions that might lead to unintended results.

During a much earlier review of this system, our human factors specialist identified some concerns in regard to ease of use of the device that we communicated to the PMA sponsor. These were in the context of a review of the device in an early draft of the labeling and the safety report. We are now reviewing findings from the pivotal clinical study to see if anything else can be learned about this aspect of device use.

We expect that any remaining human factors concerns can be resolved with labeling improvements or changes to the training program for the product. We also typically see improvements in human factors features as products hit the marketplace and the PMA sponsor gets feedback from customers. We would review these changes as PMA supplements down the road.

Finally, I would like to speak briefly about

device accuracy. The sponsor provided data for the various aspects of accuracy. This was derived from piglet and human neonate and infant studies. As you know, the fetal oxygen saturation value taken from this system can't be compared to a fetal co-oximeter reading because it is not practical to obtain a fetal arterial blood sample. Therefore, reading comparisons could not be conducted in humans at the 20-50 percent oxygen saturation levels of interest. Accuracy estimates are, thus, limited in this respect. We accept this as unavoidable.

We also continued to work with the PMA sponsor to translate bias and precision data into a clinically meaningful expression that is understandable by the healthcare provider, for example obstetricians, family practice physicians, nurse and nurse midwives, who may not understand these statistical terms.

Our clinical reviewer, Dr. Mitchell, whose talk will immediately follow mine, will continue the discussion of accuracy in her presentation.

So to conclude, you should know that we will continue to work with the company to resolve these issues in areas of product safety, including human factors and accuracy.

I will take questions when the panel Chair would like to entertain them, now or at the end of Dr. Mitchell's

talk.

CHAIRMAN BLANCO: Let's go ahead and have the questions now, if there are any. There don't appear to be any. We will continue. Thank you.

MS. DAWS-KOPP: Okay. Now I would like to introduce Dr. Mitchell, the clinical reviewer on this PMA.

Clinical Aspects

DR. MITCHELL: Good morning. Thank you, Ms. Daws-Kopp, for the review of the preclinical issues that we continue to look at.

My job today is to review the clinical study results. The FDA review of the clinical data is ongoing. The purpose of my discussion is to point out the outstanding issues and ask the panel to comment on them within the context of the data as presented by the company.

The issues that I will be discussing today include the clinical use characteristics, the study objectives, the unanticipated finding of the cesarean section rates for dystocia. I will do a brief comparison of the baseline versus the randomized, controlled trial, and then I will touch on the labeling.

The clinical use characteristics that I am going to discuss today include the 30 percent FSpO2 threshold, and FSpO2 means the saturation as measured by the sensor; the bias and precision; the management matrix; and the

registration time.

Dr. Swedlow did a nice review of how the 30 percent threshold was determined. I will just go back over that quickly. First, there was a literature search of animal investigations, followed by the prospective demonstration of the 30 percent threshold in a fetal sheep model, and then the prospective study in human fetuses.

This prospective human study was a measurement of the relationship between fetal oxygen saturation and fetal scalp pH, with acidosis being defined as a pH of less than 7.2.

There were 46 subjects, laboring patients, and to paired data points. Some subjects had more than one data point. As a result of this study, they found that the sensitivity of the device -- I have a laser pointer but I am afraid to use it because of the say the room is structured, so bear with me a little bit. They found that the sensitivity of the device was 81 percent so that in the 16 data points where the pH was less than 7.2, in 13 of those pairs the oximeter reading also was less than 30 percent. The specificity was 100 percent, which meant that of the 34 pHs that were greater than 7.2, all 34 oximeter readings were greater than 30 percent.

Next, the company went on to look at the bias and precision of the device. SaO2 is blood saturation. And, in

the first study listed up there, in an animal piglet model the observed average bias between individual readings of the SaO2 and the FSpO2, in the range of 15-40 percent, was minus 0.6 percent, with a standard deviation of 4.8 percent.

They did the same study in sick infants and children and found that the average bias was in the same direction, minus 1.9 percent, with a standard deviation of 5.4 percent.

Then, the precision of the device was examined, and the precision was measured as the standard deviation between two devices measuring oxygenation at the same time from the same fetus, and the precision was 4.7 percent.

The sponsor concludes with this summarizing statement: The average difference between FSpO2 from the N-400 and blood SaO2, in the range of 15 and 40 percent is 0.6 percent, and the typical variation between these readings is 4.7 percent. Thus, for example, at a true fetal SaO2 of 30 percent, two-thirds of the FSpO2 readings can be expected to fall between 25 percent and 34 percent.

This also means that at a fetal SaO2 of 30 percent, 95 percent of the FSpO2 readings can be expected to fall between 20 and 40 percent.

Next, I would like to briefly review for you the management matrix for the algorithm for evaluating the fetal heart rate tracings that was used during the study and that

is also in the labeling.

The company defined the FSpO2 as non-reassuring when the FSpO2 remains below 30 percent between contractions, or no value is available despite sensor adjustment. And, FSpO2 was defined as reassuring when it returns to a value of greater than or equal to 30 percent between contractions.

This is a histogram showing the distribution of registration times. Each bar represents 5 percent. So, if you look at the pink bar at the far left, 5 of the patients had the sensor give a reading during 5 percent of their labor. If you look at the light yellow bar on the far right of the tracing, 15 of the patients had the sensor produce a reading 100 percent of the time during their labor. The median registration time then was 67 percent. As you can see, it is not a normal distribution.

So, this meant that 50 percent of the patients had a reading present two-thirds of the time during their labor. Conversely, 50 percent of the patients had a reading present less than two-thirds of the time during their labor.

So in summary, the clinical use characteristics I have highlighted include the 30 percent FSpO2 threshold; precision and bias; management matrix; and registration time. That will be part of a discussion question.

In the next part of my talk I will review the

study objectives, as well as the results from the study objectives. There were three objectives to the study. The primary objective was for effectiveness, and it was to reduce the cesarean sections for non-reassuring fetal status, as already stated.

Then, there were two safety objectives, that labor would be safe to continue if the oxygen saturation was above 30 percent, and that use of the sensor was safe for the mother and the fetus.

Before I describe the results as they relate to these three specific objectives, I would just like to take a look at the overall cesarean section rate. As you can see, these are rates so it is reported as a percentage between the test and control group. The test group is on the left and reads as FHR plus FSpO2. The control group is on the right. And, the cesarean section rates were essentially the same, at 26 percent and 29 percent.

This is a histogram. It doesn't report rates; it reports the actual number of patients on the vertical axis for the test and control groups, and this is for cesarean sections for non-reassuring fetal status. As we can see, there is a difference. There were 23 cesarean sections for NRFS in the test group and 51 in the control group.

The sponsor then spent some time discussing the sensitivity and specificity of the device. The comment I